OLANZAPINE- olanzapine injection, powder, for solution
TYA Pharmaceuticals

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Olanzapine for Injection safely and effectively. See full prescribing information for Olanzapine for Injection. Olanzapine for Injection, Powder, For Solution for Intramuscular use Initial U.S. Approval: 1996

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Olanzapine for Injection is not approved for the treatment of patients with dementia-related psychosis. (5.1, 5.14, 17.2)**

RECENT MAJOR CHANGES

None

INDICATIONS AND USAGE

Olanzapine for Injection is an atypical antipsychotic indicated: (1)

- Treatment of acute agitation associated with schizophrenia and bipolar I mania. (1.4)
- Efficacy was established in three 1-day trials in adults. (14.3)

DOSAGE AND ADMINISTRATION

Agitation associated with Schizophrenia and Bipolar I Mania in adults (2.4) (2)	IM: 10 mg (5 mg or 7.5 mg when clinically warranted) Assess for orthostatic hypotension prior to subsequent dosing (max. 3 doses 2 to 4 hrs apart)

DOSAGE FORMS AND STRENGTHS

- Intramuscular Injection: 10 mg vial (3)

CONTRAINDICATIONS

- None with Olanzapine monotherapy.
- When using Olanzapine in combination with lithium or valproate, refer to the Contraindications section of the package inserts for those products. (4)

WARNINGS AND PRECAUTIONS

- Increased risk of death and increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack). (5.1) *Elderly Patients with Dementia-Related Psychosis:*
- The possibility of a suicide attempt is inherent in schizophrenia and in bipolar I disorder, and close supervision of high-risk patients should accompany drug therapy.(5.2) *Suicide:*
- Manage with immediate discontinuation and close monitoring. (5.3) *Neuroleptic Malignant Syndrome:*
- In some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients taking olanzapine. Patients taking olanzapine should be monitored for symptoms of hyperglycemia and undergo fasting blood glucose testing at the beginning of, and periodically during, treatment. (5.4) *Hyperglycemia:*
- Undesirable alterations in lipids have been observed. Appropriate clinical monitoring is recommended, including fasting blood lipid testing at the beginning of, and periodically during, treatment. (5.5) *Hyperlipidemia:*
- Potential consequences of weight gain should be considered. Patients should receive regular monitoring of weight. (5.6) *Weight Gain:*
- Discontinue if clinically appropriate. (5.7) *Tardive Dyskinesia:*
- Orthostatic hypotension associated with dizziness, tachycardia, bradycardia and, in some patients, syncope, may occur especially during initial dose titration. Use caution in patients with cardiovascular disease, cerebrovascular disease, and those conditions that could affect hemodynamic responses. (5.8) *Orthostatic Hypotension:*
- Has been reported with antipsychotics, including Olanzapine for Injection. Patients with a history of a clinically significant low white blood cell count (WBC) or drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of Olanzapine for Injection

should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors. (5.9) *Leukopenia, Neutropenia, and Agranulocytosis:*

- Use cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold. (5.11) *Seizures:*
- Has potential to impair judgment, thinking, and motor skills. Use caution when operating machinery. (5.12) *Potential for Cognitive and Motor Impairment:*
- May elevate prolactin levels. (5.15) *Hyperprolactinemia:*
- . (5.16) *Use in Combination with, Lithium or Valproate*
- Monitor fasting blood glucose and lipid profiles at the beginning of, and periodically during, treatment. (5.17) *Laboratory Tests:*

ADVERSE REACTIONS

Most common adverse reactions (≥5% and at least twice that for placebo) associated with:
Oral Olanzapine Monotherapy:

- - postural hypotension, constipation, weight gain, dizziness, personality disorder, akathisia (6.1) Schizophrenia (Adults)
- - sedation, weight increased, headache, increased appetite, dizziness, abdominal pain, pain in extremity, fatigue, dry mouth (6.1) Schizophrenia (Adolescents)
- – asthenia, dry mouth, constipation, increased appetite, somnolence, dizziness, tremor (6.1) Manic or Mixed Episodes, Bipolar I Disorder (Adults)
- – sedation, weight increased, increased appetite, headache, fatigue, dizziness, dry mouth, abdominal pain, pain in extremity (6.1) Manic or Mixed Episodes, Bipolar I Disorder (Adolescents)

Combination of Olanzapine and Lithium or Valproate:

- – dry mouth, weight gain, increased appetite, dizziness, back pain, constipation, speech disorder, increased salivation, amnesia, paresthesia (6.1) Manic or Mixed Episodes, Bipolar I Disorder (Adults)

Olanzapine for Injection:

- – somnolence (6.1) Agitation with Schizophrenia and Bipolar I Mania (Adults)

To report SUSPECTED ADVERSE REACTIONS, contact Sandoz Inc. at or FDA at 1-800-FDA-1088 or 1-800-525-8747www.fda.gov/medwatch

DRUG INTERACTIONS

- May potentiate orthostatic hypotension. (7.1, 7.2) *Diazepam:*
- May potentiate orthostatic hypotension. (7.1) *Alcohol:*
- Increased clearance of olanzapine. (7.1) *Carbamazepine:*
- May increase olanzapine levels. (7.1) *Fluvoxamine:*
- Caution should be used when taken in combination with other centrally acting drugs and alcohol. (7.2) *CNS Acting Drugs:*
- Enhanced antihypertensive effect. (7.2) *Antihypertensive Agents:*
- May antagonize levodopa/dopamine agonists. (7.2) *Levodopa and Dopamine Agonists:*
- Increased somnolence with IM olanzapine. (7.2) *Lorazepam (IM):*
- When using olanzapine in combination with lithium or valproate, refer to the Drug Interactions sections of the package insert for those products. (7.2) *Other Concomitant Drug Therapy:*

USE IN SPECIFIC POPULATIONS

- Olanzapine for Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1) *Pregnancy:*
- Breast-feeding is not recommended. (8.3) *Nursing Mothers:*
- Safety and effectiveness of Olanzapine for Injection in children <18 years of age have not been established. (8.4) *Pediatric Use:*

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 9/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Olanzapine for Injection is not approved for the treatment of patients with dementia-related psychosis WARNINGS AND PRECAUTIONS (,) AND PATIENT COUNSELING INFORMATION ( ) . *[see* 5.15.1417.2*]*

1 INDICATIONS AND USAGE

1.4 Olanzapine for Injection Agitation Associated with Schizophrenia and Bipolar I Mania

Olanzapine for Injection is indicated for the treatment of acute agitation associated with schizophrenia and bipolar I mania.

Efficacy was demonstrated in 3 short-term (24 hours of IM treatment) placebo-controlled trials in agitated adult inpatients with: schizophrenia or bipolar I disorder (manic or mixed episodes) *[see* **CLINICAL STUDIES ( ) 14.3***]*.

“Psychomotor agitation” is defined in DSM-IV as “excessive motor activity associated with a feeling of inner tension.” Patients experiencing agitation often manifest behaviors that interfere with their

diagnosis and care, e.g., threatening behaviors, escalating or urgently distressing behavior, or self-exhausting behavior, leading clinicians to the use of intramuscular antipsychotic medications to achieve immediate control of the agitation.

2 DOSAGE AND ADMINISTRATION

2.4 Olanzapine for Injection: Agitation Associated with Schizophrenia and Bipolar I Mania

Dose Selection for Agitated Adult Patients with Schizophrenia and Bipolar I Mania

The efficacy of intramuscular olanzapine for injection in controlling agitation in these disorders was demonstrated in a dose range of 2.5 mg to 10 mg. The recommended dose in these patients is 10 mg. A lower dose of 5 or 7.5 mg may be considered when clinical factors warrant . If agitation warranting additional intramuscular doses persists following the initial dose, subsequent doses up to 10 mg may be given. However, the efficacy of repeated doses of intramuscular olanzapine for injection in agitated patients has not been systematically evaluated in controlled clinical trials. Also, the safety of total daily doses greater than 30 mg, or 10 mg injections given more frequently than 2 hours after the initial dose, and 4 hours after the second dose have not been evaluated in clinical trials. Maximal dosing of intramuscular olanzapine (e.g., 3 doses of 10 mg administered 2 to 4 hours apart) may be associated with a substantial occurrence of significant orthostatic hypotension Thus, it is recommended that patients requiring subsequent intramuscular injections be assessed for orthostatic hypotension prior to the administration of any subsequent doses of intramuscular olanzapine for injection. The administration of an additional dose to a patient with a clinically significant postural change in systolic blood pressure is not recommended. *[see* **CLINICAL STUDIES ( ) 14.3***][see* **WARNINGS AND PRECAUTIONS ( ) 5.8***]*.

If ongoing olanzapine therapy is clinically indicated, oral olanzapine may be initiated in a range of 5 to 20 mg/day as soon as clinically appropriate .

Intramuscular Dosing in Special Populations

A dose of 5 mg/injection should be considered for geriatric patients or when other clinical factors warrant. A lower dose of 2.5 mg/injection should be considered for patients who otherwise might be debilitated, be predisposed to hypotensive reactions, or be more pharmacodynamically sensitive to olanzapine AND . *[see* **WARNINGS AND PRECAUTIONS ( ), DRUG INTERACTIONS ( ), 5.147CLINICAL PHARMACOLOGY ( ) 12.3***]*

Administration of Olanzapine for Injection

Olanzapine for Injection is intended for intramuscular use only. Do not administer intravenously or subcutaneously. Inject slowly, deep into the muscle mass.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Directions for Preparation of Olanzapine for Injection with Sterile Water for Injection

Dissolve the contents of the vial using 2.1 mL of Sterile Water for Injection to provide a solution containing approximately 5 mg/mL of olanzapine. The resulting solution should appear clear and yellow. Olanzapine for Injection reconstituted with Sterile Water for Injection should be used immediately (within 1 hour) after reconstitution. *Discard any unused portion.*

The following table provides injection volumes for delivering various doses of intramuscular olanzapine for injection reconstituted with Sterile Water for Injection.

Dose, mg Olanzapine	Volume of Injection, mL
10	Withdraw total contents of vial
7.5	1.5

5	1
2.5	0.5

Physical Incompatibility Information

Olanzapine for Injection should be reconstituted only with Sterile Water for Injection. Olanzapine for Injection should not be combined in a syringe with diazepam injection because precipitation occurs when these products are mixed. Lorazepam injection should not be used to reconstitute Olanzapine for Injection as this combination results in a delayed reconstitution time. Olanzapine for Injection should not be combined in a syringe with haloperidol injection because the resulting low pH has been shown to degrade olanzapine over time.

3 DOSAGE FORMS AND STRENGTHS

Olanzapine for Injection is available in 10 mg vial (1s).

4 CONTRAINDICATIONS

- None with Olanzapine for Injection monotherapy.
- For specific information about the contraindications of lithium or valproate, refer to the Contraindications section of the package inserts for these other products.

5 WARNINGS AND PRECAUTIONS

5.1 Elderly Patients with Dementia-Related Psychosis

Increased Mortality

AND . **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Olanzapine for Injection is not approved for the treatment of patients with dementia-related psychosis** *[see* **BOXED WARNING, WARNINGS AND PRECAUTIONS ( ) 5.14PATIENT COUNSELING INFORMATION ( ) 17.2***]*

In placebo-controlled clinical trials of elderly patients with dementia-related psychosis, the incidence of death in olanzapine-treated patients was significantly greater than placebo-treated patients (3.5% vs 1.5%, respectively).

Cerebrovascular Adverse Events (CVAE), Including Stroke

Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients in trials of olanzapine in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis . *[see* **BOXED WARNING AND PATIENT COUNSELING INFORMATION ( ) 17.2***]*

5.2 Suicide

The possibility of a suicide attempt is inherent in schizophrenia and in bipolar I disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for olanzapine should be written for the smallest quantity consistent with good patient management, in order to reduce the risk of overdose.

5.3 Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including olanzapine.

Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported . *[see* **PATIENT COUNSELING INFORMATION ( ) 17.3***]*

5.4 Hyperglycemia

Physicians should consider the risks and benefits when prescribing olanzapine to patients with an established diagnosis of diabetes mellitus, or having borderline increased blood glucose level (fasting 100 to 126 mg/dL, nonfasting 140 to 200 mg/dL). Patients taking olanzapine should be monitored regularly for worsening of glucose control. Patients starting treatment with olanzapine should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug . *[see* **PATIENT COUNSELING INFORMATION ( ) 17.4***]*

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including olanzapine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics. While relative risk estimates are inconsistent, the association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics.

Mean increases in blood glucose have been observed in patients treated (median exposure of 9.2 months) with olanzapine in phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). The mean increase of serum glucose (fasting and nonfasting samples) from baseline to the average of the 2 highest serum concentrations was 15 mg/dL.

In a study of healthy volunteers, subjects who received olanzapine (N=22) for 3 weeks had a mean increase compared to baseline in fasting blood glucose of 2.3 mg/dL. Placebo-treated subjects (N=19) had a mean increase in fasting blood glucose compared to baseline of 0.34 mg/dL.

Olanzapine Monotherapy in Adults

In an analysis of 5 placebo-controlled adult olanzapine monotherapy studies with a median treatment duration of approximately 3 weeks, olanzapine was associated with a greater mean change in fasting

glucose levels compared to placebo (2.76 mg/dL versus 0.17 mg/dL). The difference in mean changes between olanzapine and placebo was greater in patients with evidence of glucose dysregulation at baseline (patients diagnosed with diabetes mellitus or related adverse reactions, patients treated with anti-diabetic agents, patients with a baseline random glucose level ≥200 mg/dL, and/or a baseline fasting glucose level ≥126 mg/dL). Olanzapine-treated patients had a greater mean HbA1c increase from baseline of 0.04% (median exposure 21 days), compared to a mean HbA1c decrease of 0.06% in placebo-treated subjects (median exposure 17 days).

In an analysis of 8 placebo-controlled studies (median treatment exposure 4 to 5 weeks), 6.1% of olanzapine-treated subjects (N=855) had treatment-emergent glycosuria compared to 2.8% of placebo-treated subjects (N=599). shows short-term and long-term changes in fasting glucose levels from adult olanzapine monotherapy studies. **Table 2**

Table 2: Changes in Fasting Glucose Levelsfrom Adult Olanzapine Monotherapy Studies

			Up to 12 weeks exposure		**At least 48 weeks exposure**	
Laboratory Analyte	**Category Change (at least once) from Baseline**	**Treatment Arm**	**N**	**Patients**	**N**	**Patients**
Fasting Glucose	Normal to High (<100 mg/dL to ≥126 mg/dL)	Olanzapine	543	2.2%	345	12.8%
		Placebo	293	3.4%	NA [a]	NA [a]
	Borderline to High (≥100 mg/dL and <126 mg/dL to ≥126 mg/dL)	Olanzapine	178	17.4%	127	26%
		Placebo	96	11.5%	NA [a]	NA [a]

Not Applicable. [a]

The mean change in fasting glucose for patients exposed at least 48 weeks was 4.2 mg/dL (N=487). In analyses of patients who completed 9 to 12 months of olanzapine therapy, mean change in fasting and nonfasting glucose levels continued to increase over time.

Olanzapine Monotherapy in Adolescents

The safety and efficacy of olanzapine for injection have not been established in patients under the age of 18 years. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescent patients, including those with schizophrenia (6 weeks) or bipolar I disorder (manic or mixed episodes) (3 weeks), olanzapine was associated with a greater mean change from baseline in fasting glucose levels compared to placebo (2.68 mg/dL versus -2.59 mg/dL). The mean change in fasting glucose for adolescents exposed at least 24 weeks was 3.1 mg/dL (N=121). shows short-term and long-term changes in fasting blood glucose from adolescent olanzapine monotherapy studies. **Table 3**

Table 3: Changes in Fasting Glucose Levels fromAdolescent Olanzapine Monotherapy Studies

	Up to 12	**At least 24**

			weeks exposure		weeks exposure	
Laboratory Analyte	**Category Change (at least once) from Baseline**	**Treatment Arm**	**N**	**Patients**	**N**	**Patients**
Fasting Glucose	Normal to High (<100 mg/dL to ≥126 mg/dL)	Olanzapine	124	0%	108	0.9%
		Placebo	53	1.9%	NA [a]	NA [a]
	Borderline to High (≥100 mg/dL and <126 mg/dL to ≥126 mg/dL)	Olanzapine	14	14.3%	13	23.1%
		Placebo	13	0%	NA [a]	NA [a]

Not Applicable. [a]

5.5 Hyperlipidemia

Undesirable alterations in lipids have been observed with olanzapine use. Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using olanzapine, is recommended . *[see* **PATIENT COUNSELING INFORMATION ( ) 17.5***]*

Clinically significant, and sometimes very high (>500 mg/dL), elevations in triglyceride levels have been observed with olanzapine use. Modest mean increases in total cholesterol have also been seen with olanzapine use.

Olanzapine Monotherapy in Adults

In an analysis of 5 placebo-controlled olanzapine monotherapy studies with treatment duration up to 12 weeks, olanzapine-treated patients had increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 5.3 mg/dL, 3 mg/dL, and 20.8 mg/dL respectively compared to decreases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 6.1 mg/dL, 4.3 mg/dL, and 10.7 mg/dL for placebo-treated patients. For fasting HDL cholesterol, no clinically meaningful differences were observed between olanzapine-treated patients and placebo-treated patients. Mean increases in fasting lipid values (total cholesterol, LDL cholesterol, and triglycerides) were greater in patients without evidence of lipid dysregulation at baseline, where lipid dysregulation was defined as patients diagnosed with dyslipidemia or related adverse reactions, patients treated with lipid lowering agents, or patients with high baseline lipid levels.

In long-term studies (at least 48 weeks), patients had increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 5.6 mg/dL, 2.5 mg/dL, and 18.7 mg/dL, respectively, and a mean decrease in fasting HDL cholesterol of 0.16 mg/dL. In an analysis of patients who completed 12 months of therapy, the mean nonfasting total cholesterol did not increase further after approximately 4 to 6 months.

The proportion of patients who had changes (at least once) in total cholesterol, LDL cholesterol or triglycerides from normal or borderline to high, or changes in HDL cholesterol from normal or borderline to low, was greater in long-term studies (at least 48 weeks) as compared with short-term studies. shows categorical changes in fasting lipids values. **Table 4**

Table 4: Changes in Fasting Lipids Values from AdultOlanzapine Monotherapy Studies

			Up to 12 weeks exposure		At least 48 weeks exposure	
Laboratory Analyte	**Category Change (at least once) from Baseline**	**Treatment Arm**	**N**	**Patients**	**N**	**Patients**
Fasting Triglycerides	Increase by ≥50 mg/dL	Olanzapine	745	39.6%	487	61.4%
		Placebo	402	26.1%	NA [a]	NA [a]
	Normal to High (<150 mg/dL to ≥200 mg/dL)	Olanzapine	457	9.2%	293	32.4%
		Placebo	251	4.4%	NA [a]	NA [a]
	Borderline to High (≥150 mg/dL and <200 mg/dL to ≥200 mg/dL)	Olanzapine	135	39.3%	75	70.7%
		Placebo	65	20%	NA [a]	NA [a]
Fasting Total Cholesterol	Increase by ≥40 mg/dL	Olanzapine	745	21.6%	489	32.9%
		Placebo	402	9.5%	NA [a]	NA [a]
	Normal to High (<200 mg/dL to ≥240 mg/dL)	Olanzapine	392	2.8%	283	14.8%
		Placebo	207	2.4%	NA [a]	NA [a]
	Borderline to High (≥200 mg/dL and <240 mg/dL to ≥240 mg/dL)	Olanzapine	222	23%	125	55.2%
		Placebo	112	12.5%	NA [a]	NA [a]
Fasting LDL Cholesterol	Increase by ≥30 mg/dL	Olanzapine	536	23.7%	483	39.8%
		Placebo	304	14.1%	NA [a]	NA [a]
	Normal to High (<100 mg/dL to ≥160 mg/dL)	Olanzapine	154	0%	123	7.3%
		Placebo	82	1.2%	NA [a]	NA [a]
	Borderline to High (≥100 mg/dL and <160 mg/dL to ≥160 mg/dL)	Olanzapine	302	10.6%	284	31%
		Placebo	173	8.1%	NA [a]	NA [a]

Not Applicable. [a]

In phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), over a median exposure of 9.2 months, the mean increase in triglycerides in patients taking olanzapine was 40.5 mg/dL.

In phase 1 of CATIE, the mean increase in total cholesterol was 9.4 mg/dL.

Olanzapine Monotherapy in Adolescents

The safety and efficacy of olanzapine for injection have not been established in patients under the age of 18 years. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescents, including those with schizophrenia (6 weeks) or bipolar I disorder (manic or mixed episodes) (3 weeks), olanzapine-treated adolescents had increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 12.9 mg/dL, 6.5 mg/dL, and 28.4 mg/dL, respectively, compared to increases from baseline in mean fasting total cholesterol and LDL cholesterol of 1.3 mg/dL and 1mg/dL, and a decrease in triglycerides of 1.1 mg/dL for placebo-treated adolescents. For fasting HDL cholesterol, no clinically meaningful differences were observed between olanzapine-treated adolescents and placebo-treated adolescents.

In long-term studies (at least 24 weeks), adolescents had increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 5.5 mg/dL, 5.4 mg/dL, and 20.5 mg/dL, respectively, and a mean decrease in fasting HDL cholesterol of 4.5 mg/dL. shows categorical changes in fasting lipids values in adolescents. **Table 5**

Table 5: Changes in Fasting Lipids Values from Adolescent Olanzapine Monotherapy Studies

			Up to 6 weeks exposure		**At least 24 weeks exposure**	
Laboratory Analyte	**Category Change (at least once) from Baseline**	**Treatment Arm**	**N**	**Patients**	**N**	**Patients**
Fasting Triglycerides	Increase by ≥50 mg/dL	Olanzapine	138	37%	122	45.9%
		Placebo	66	15.2%	NA [a]	NA [a]
	Normal to High (<90 mg/dL to >130 mg/dL)	Olanzapine	67	26.9%	66	36.4%
		Placebo	28	10.7%	NA [a]	NA [a]
	Borderline to High (≥90 mg/dL and ≤130 mg/dL to >130 mg/dL)	Olanzapine	37	59.5%	31	64.5%
		Placebo	17	35.3%	NA [a]	NA [a]
Fasting Total Cholesterol	Increase by ≥40 mg/dL	Olanzapine	138	14.5%	122	14.8%
		Placebo	66	4.5%	NA [a]	NA [a]
	Normal to High (<170 mg/dL to ≥200 mg/dL)	Olanzapine	87	6.9%	78	7.7%
		Placebo	43	2.3%	NA [a]	NA [a]
	Borderline to High (≥170 mg/dL and <200 mg/dL to ≥200	Olanzapine	36	38.9%	33	57.6%
		Placebo	13	7.7%	NA [a]	NA [a]

	mg/dL)					
Fasting LDL Cholesterol	Increase by ≥30 mg/dL	Olanzapine	137	17.5%	121	22.3%
		Placebo	63	11.1%	NA [a]	NA [a]
	Normal to High (<110 mg/dL to ≥130 mg/dL)	Olanzapine	98	5.1%	92	10.9%
		Placebo	44	4.5%	NA [a]	NA [a]
	Borderline to High (≥110 mg/dL and <130 mg/dL to ≥130 mg/dL)	Olanzapine	29	48.3%	21	47.6%
		Placebo	9	0%	NA [a]	NA [a]

Not Applicable. [a]

5.6 Weight Gain

Potential consequences of weight gain should be considered prior to starting olanzapine. Patients receiving olanzapine should receive regular monitoring of weight . *[see* **PATIENT COUNSELING INFORMATION ( ) 17.6***]*

Olanzapine Monotherapy in Adults

In an analysis of 13 placebo-controlled olanzapine monotherapy studies, olanzapine-treated patients gained an average of 2.6 kg (5.7 lb) compared to an average 0.3 kg (0.6 lb) weight loss in placebo-treated patients with a median exposure of 6 weeks; 22.2% of olanzapine-treated patients gained at least 7% of their baseline weight, compared to 3% of placebo-treated patients, with a median exposure of 8 weeks; 4.2% of olanzapine-treated patients gained at least 15% of their baseline weight, compared to 0.3% of placebo-treated patients, with a median exposure to event of 12 weeks. Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories. Discontinuation due to weight gain occurred in 0.2% of olanzapine-treated patients and in 0% of placebo-treated patients.

In long-term studies (at least 48 weeks), the mean weight gain was 5.6 kg (12.3 lb) (median exposure of 573 days, N=2021). The percentages of patients who gained at least 7%, 15%, or 25% of their baseline body weight with long-term exposure were 64%, 32%, and 12%, respectively. Discontinuation due to weight gain occurred in 0.4% of olanzapine-treated patients following at least 48 weeks of exposure.

includes data on adult weight gain with olanzapine pooled from 86 clinical trials. The data in each column represent data for those patients who completed treatment periods of the durations specified.
Table 6

Table 6: Weight Gain with Olanzapine Use in Adults

Amount Gained kg (lb)	**6 Weeks (N=7465) (%)**	**6 Months (N=4162) (%)**	**12 Months (N=1345) (%)**	**24 Months (N=474) (%)**	**36 Months (N=147) (%)**
≤0	26.2	24.3	20.8	23.2	17
0 to ≤5 (0-11 lb)	57	36	26	23.4	25.2
>5 to ≤10 (11-22 lb)	14.9	24.6	24.2	24.1	18.4

>10 to ≤15 (22-33 lb)	1.8	10.9	14.9	11.4	17
>15 to ≤20 (33-44 lb)	0.1	3.1	8.6	9.3	11.6
>20 to ≤25 (44-55 lb)	0	0.9	3.3	5.1	4.1
>25 to ≤30 (55-66 lb)	0	0.2	1.4	2.3	4.8
>30 (>66 lb)	0	0.1	0.8	1.2	2

Olanzapine Monotherapy in Adolescents

The safety and efficacy of olanzapine for injection have not been established in patients under the age of 18 years. Mean increase in weight in adolescents was greater than in adults. In 4 placebo-controlled trials, discontinuation due to weight gain occurred in 1% of olanzapine-treated patients, compared to 0% of placebo-treated patients.

Table 7: Weight Gain with Olanzapine Use inAdolescents from 4 Placebo-Controlled Trials

	Olanzapine-treated patients	**Placebo-treated patients**
(median exposure = 3 weeks) Mean change in body weight from baseline	4.6 kg (10.1 lb)	0.3 kg (0.7 lb)
Percentage of patients who gained at least 7% of baseline body weight	(median exposure to 7% = 4 weeks) 40.6%	(median exposure to 7% = 8 weeks) 9.8%
Percentage of patients who gained at least 15% of baseline body weight	(median exposure to 15% = 19 weeks) 7.1%	(median exposure to 15% = 8 weeks) 2.7%

In long-term studies (at least 24 weeks), the mean weight gain was 11.2 kg (24.6 lb); (median exposure of 201 days, N=179). The percentages of adolescents who gained at least 7%, 15%, or 25% of their baseline body weight with long-term exposure were 89%, 55%, and 29%, respectively. Among adolescent patients, mean weight gain by baseline BMI category was 11.5 kg (25.3 lb), 12.1 kg (26.6 lb), and 12.7 kg (27.9 lb), respectively, for normal (N=106), overweight (N=26) and obese (N=17). Discontinuation due to weight gain occurred in 2.2% of olanzapine-treated patients following at least 24 weeks of exposure.

shows data on adolescent weight gain with olanzapine pooled from 6 clinical trials. The data in each column represent data for those patients who completed treatment periods of the durations specified. Little clinical trial data is available on weight gain in adolescents with olanzapine beyond 6 months of treatment. **Table 8**

Table 8: Weight Gain with Olanzapine Use in Adolescents

Amount Gained kg (lb)	**6 Weeks (N=243) (%)**	**6 Months (N=191) (%)**

≤0	2.9	2.1
0 to ≤5 (0-11 lb)	47.3	24.6
>5 to ≤10 (11-22 lb)	42.4	26.7
>10 to ≤15 (22-33 lb)	5.8	22
>15 to ≤20 (33-44 lb)	0.8	12.6
>20 to ≤25 (44-55 lb)	0.8	9.4
>25 to ≤30 (55-66 lb)	0	2.1
>30 to ≤35 (66-77 lb)	0	0
>35 to ≤40 (77-88 lb)	0	0
>40 (>88 lb)	0	0.5

5.7 Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses or may even arise after discontinuation of treatment.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, olanzapine should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients (1) who suffer from a chronic illness that is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on olanzapine, drug discontinuation should be considered. However, some patients may require treatment with olanzapine despite the presence of the syndrome.

For specific information about the warnings of lithium or valproate, refer to the Warnings section of the package inserts for these other products.

5.8 Orthostatic Hypotension

Olanzapine may induce orthostatic hypotension associated with dizziness, tachycardia, bradycardia and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α -adrenergic antagonistic properties . $_1$*[see* **PATIENT COUNSELING INFORMATION ( ) 17.7***]*

For oral olanzapine therapy, the risk of orthostatic hypotension and syncope may be minimized by initiating therapy with 5 mg QD . A more gradual titration to the target dose should be considered if hypotension occurs. *[see* **DOSAGE AND ADMINISTRATION (2***)]*

Hypotension, bradycardia with or without hypotension, tachycardia, and syncope were also reported

during the clinical trials with intramuscular olanzapine for injection. In an open-label clinical pharmacology study in nonagitated patients with schizophrenia in which the safety and tolerability of intramuscular olanzapine were evaluated under a maximal dosing regimen (three 10 mg doses administered 4 hours apart), approximately one-third of these patients experienced a significant orthostatic decrease in systolic blood pressure (i.e., decrease ≥30 mmHg) . Syncope was reported in 0.6% (15/2500) of olanzapine-treated patients in phase 2 to 3 oral olanzapine studies and in 0.3% (2/722) of olanzapine-treated patients with agitation in the intramuscular olanzapine for injection studies. Three normal volunteers in phase 1 studies with intramuscular olanzapine experienced hypotension, bradycardia, and sinus pauses of up to 6 seconds that spontaneously resolved (in 2 cases the reactions occurred on intramuscular olanzapine, and in 1 case, on oral olanzapine). The risk for this sequence of hypotension, bradycardia, and sinus pause may be greater in nonpsychiatric patients compared to psychiatric patients who are possibly more adapted to certain effects of psychotropic drugs. For intramuscular Olanzapine for Injection therapy, patients should remain recumbent if drowsy or dizzy after injection until examination has indicated that they are not experiencing postural hypotension, bradycardia, and/or hypoventilation. *[see* **DOSAGE AND ADMINISTRATION ( ) 2.4***]*

Olanzapine should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications) where the occurrence of syncope, or hypotension and/or bradycardia might put the patient at increased medical risk.

Caution is necessary in patients who receive treatment with other drugs having effects that can induce hypotension, bradycardia, respiratory or central nervous system depression . Concomitant administration of intramuscular olanzapine and parenteral benzodiazepine is not recommended due to the potential for excessive sedation and cardiorespiratory depression. *[see* **DRUG INTERACTIONS ( ) 7***]*

5.9 Leukopenia, Neutropenia, and Agranulocytosis

Class Effect

In clinical trial and/or postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including Olanzapine for Injection. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of Olanzapine for Injection should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm) should discontinue Olanzapine for Injection and have their WBC followed until recovery. [3]

5.10 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's disease. Olanzapine is not approved for the treatment of patients with Alzheimer's disease.

5.11 Seizures

During premarketing testing, seizures occurred in 0.9% (22/2500) of olanzapine-treated patients. There were confounding factors that may have contributed to the occurrence of seizures in many of these cases. Olanzapine should be used cautiously in patients with a history of seizures or with conditions that

potentially lower the seizure threshold, e.g., Alzheimer's dementia. Olanzapine is not approved for the treatment of patients with Alzheimer's disease. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

5.12 Potential for Cognitive and Motor Impairment

Somnolence was a commonly reported adverse reaction associated with olanzapine treatment, occurring at an incidence of 26% in olanzapine patients compared to 15% in placebo patients. This adverse reaction was also dose related. Somnolence led to discontinuation in 0.4% (9/2500) of patients in the premarketing database.

Since olanzapine has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that olanzapine therapy does not affect them adversely . *[see* **PATIENT COUNSELING INFORMATION ( ) 17.8***]*

5.13 Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing olanzapine for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration . *[see* **PATIENT COUNSELING INFORMATION ( ) 17.9***]*

5.14 Use in Patients with Concomitant Illness

Clinical experience with olanzapine in patients with certain concomitant systemic illnesses is limited . *[see* **CLINICAL PHARMACOLOGY ( ) 12.3***]*

Olanzapine exhibits muscarinic receptor affinity. In premarketing clinical trials with olanzapine, olanzapine was associated with constipation, dry mouth, and tachycardia, all adverse reactions possibly related to cholinergic antagonism. Such adverse reactions were not often the basis for discontinuations from olanzapine, but olanzapine should be used with caution in patients with clinically significant prostatic hypertrophy, narrow angle glaucoma, or a history of paralytic ileus or related conditions. *in vitro*

In 5 placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis (n=1184), the following treatment-emergent adverse reactions were reported in olanzapine-treated patients at an incidence of at least 2% and significantly greater than placebo-treated patients: falls, somnolence, peripheral edema, abnormal gait, urinary incontinence, lethargy, increased weight, asthenia, pyrexia, pneumonia, dry mouth and visual hallucinations. The rate of discontinuation due to adverse reactions was greater with olanzapine than placebo (13% vs 7%). Elderly patients with dementia-related psychosis treated with olanzapine are at an increased risk of death compared to placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis AND . *[see* BOXED WARNING**, WARNINGS AND PRECAUTIONS ( ) 5.1PATIENT COUNSELING INFORMATION ( ) 17.2***]***

Olanzapine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with olanzapine, caution should be observed in cardiac patients . *[see* **WARNINGS AND PRECAUTIONS ( ) 5.8***]*

5.15 Hyperprolactinemia

As with other drugs that antagonize dopamine D receptors, olanzapine elevates prolactin levels, and the elevation persists during chronic administration. Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea,

gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects. [2]

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent , a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. As is common with compounds which increase prolactin release, an increase in mammary gland neoplasia was observed in the olanzapine carcinogenicity studies conducted in mice and rats . Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time. *in vitro[see* **NONCLINICAL TOXICOLOGY ( ) 13.1***]*

In placebo-controlled olanzapine clinical studies (up to 12 weeks), changes from normal to high in prolactin concentrations were observed in 30% of adults treated with olanzapine as compared to 10.5% of adults treated with placebo. In a pooled analysis from clinical studies including 8136 adults treated with olanzapine, potentially associated clinical manifestations included menstrual-related events (2% [49/3240] of females), sexual function-related events (2% [150/8136] of females and males), and breast-related events (0.7% [23/3240] of females, 0.2% [9/4896] of males). [123]

In placebo-controlled olanzapine monotherapy studies in adolescent patients (up to 6 weeks) with schizophrenia or bipolar I disorder (manic or mixed episodes), changes from normal to high in prolactin concentrations were observed in 47% of olanzapine-treated patients compared to 7% of placebo-treated patients. In a pooled analysis from clinical trials including 454 adolescents treated with olanzapine, potentially associated clinical manifestations included menstrual-related events (1% [2/168] of females), sexual function-related events (0.7% [3/454] of females and males), and breast-related events (2% [3/168] of females, 2% [7/286] of males) . [123]*[see* **USE IN SPECIFIC POPULATIONS ( ) 8.4***]*

Based on a search of the following terms: amenorrhea, hypomenorrhea, menstruation delayed, and oligomenorrhea. [1]

Based on a search of the following terms: anorgasmia, delayed ejaculation, erectile dysfunction, decreased libido, loss of libido, abnormal orgasm, and sexual dysfunction. [2]

Based on a search of the following terms: breast discharge, enlargement or swelling, galactorrhea, gynecomastia, and lactation disorder. [3]

5.16 Use in Combination with Lithium, or Valproate

When using Olanzapine in combination with lithium or valproate, the prescriber should refer to the Warnings and Precautions sections of the package inserts for lithium or valproate . *[see* **DRUG INTERACTIONS ( ) 7***]*

5.17 Laboratory Tests

Fasting blood glucose testing and lipid profile at the beginning of, and periodically during, treatment is recommended AND . *[see* **WARNINGS AND PRECAUTIONS (,) 5.45.5PATIENT COUNSELING INFORMATION (,) 17.417.5***]*

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect or predict the rates observed in practice.

Clinical Trials in Adults

The information below for Olanzapine is derived from a clinical trial database for Olanzapine consisting of 8661 adult patients with approximately 4165 patient-years of exposure to oral Olanzapine and 722 patients with exposure to intramuscular Olanzapine for Injection. This database includes: (1) 2500 patients who participated in multiple-dose oral olanzapine premarketing trials in schizophrenia and Alzheimer's disease representing approximately 1122 patient-years of exposure as of February 14, 1995; (2) 182 patients who participated in oral Olanzapine premarketing bipolar I disorder (manic or mixed episodes) trials representing approximately 66 patient-years of exposure; (3) 191 patients who participated in an oral Olanzapine trial of patients having various psychiatric symptoms in association with Alzheimer's disease representing approximately 29 patient-years of exposure; (4) 5788 patients from 88 additional oral Olanzapine clinical trials as of December 31, 2001; and (5) 722 patients who participated in intramuscular Olanzapine for Injection premarketing trials in agitated patients with schizophrenia, bipolar I disorder (manic or mixed episodes), or dementia. In addition, information from the premarketing 6-week clinical study database for olanzapine in combination with lithium or valproate, consisting of 224 patients who participated in bipolar I disorder (manic or mixed episodes) trials with approximately 22 patient-years of exposure, is included below.

The conditions and duration of treatment with Olanzapine varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and dose-titration studies, and short-term or longer-term exposure. Adverse reactions were assessed by collecting adverse reactions, results of physical examinations, vital signs, weights, laboratory analytes, ECGs, chest x-rays, and results of ophthalmologic examinations.

Certain portions of the discussion below relating to objective or numeric safety parameters, namely, dose-dependent adverse reactions, vital sign changes, weight gain, laboratory changes, and ECG changes are derived from studies in patients with schizophrenia and have not been duplicated for bipolar I disorder (manic or mixed episodes) or agitation. However, this information is also generally applicable to bipolar I disorder (manic or mixed episodes) and agitation.

Adverse reactions during exposure were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse reactions without first grouping similar types of reactions into a smaller number of standardized reaction categories. In the tables and tabulations that follow, MedDRA and COSTART Dictionary terminology has been used to classify reported adverse reactions.

The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse reaction of the type listed. A reaction was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. The reported reactions do not include those reaction terms that were so general as to be uninformative. Reactions listed elsewhere in labeling may not be repeated below. It is important to emphasize that, although the reactions occurred during treatment with olanzapine, they were not necessarily caused by it. The entire label should be read to gain a complete understanding of the safety profile of olanzapine.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse reactions incidence in the population studied.

Incidence of Adverse Reactions in Short-Term, Placebo-Controlled and Combination Trials

The following findings are based on premarketing trials of (1) oral olanzapine for schizophrenia, bipolar I disorder (manic or mixed episodes), a subsequent trial of patients having various psychiatric symptoms in association with Alzheimer's disease, and premarketing combination trials, and (2)

intramuscular olanzapine for injection in agitated patients with schizophrenia or bipolar I mania.

Adverse Reactions Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials

— Overall, there was no difference in the incidence of discontinuation due to adverse reactions (5% for oral olanzapine vs 6% for placebo). However, discontinuations due to increases in ALT were considered to be drug related (2% for oral olanzapine vs 0% for placebo). *Schizophrenia*

— Overall, there was no difference in the incidence of discontinuation due to adverse reactions (2% for oral olanzapine vs 2% for placebo). *Bipolar I Disorder (Manic or Mixed Episodes) Monotherapy*

- Overall, there was no difference in the incidence of discontinuation due to adverse reactions (0.4% for intramuscular olanzapine for injection vs 0% for placebo). *Agitation*

Adverse Reactions Associated with Discontinuation of Treatment in Short-Term Combination Trials

— In a study of patients who were already tolerating either lithium or valproate as monotherapy, discontinuation rates due to adverse reactions were 11% for the combination of oral olanzapine with lithium or valproate compared to 2% for patients who remained on lithium or valproate monotherapy. Discontinuations with the combination of oral olanzapine and lithium or valproate that occurred in more than 1 patient were: somnolence (3%), weight gain (1%), and peripheral edema (1%). *Bipolar I Disorder (Manic or Mixed Episodes), Olanzapine as Adjunct to Lithium or Valproate*

Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials

The most commonly observed adverse reactions associated with the use of oral olanzapine (incidence of 5% or greater) and not observed at an equivalent incidence among placebo-treated patients (olanzapine incidence at least twice that for placebo) were:

Table 9: Common Treatment-Emergent Adverse Reactions Associated with theUse of Oral Olanzapine in 6-Week Trials — SCHIZOPHRENIA

	Percentage of Patients Reporting Event	
Adverse Reaction	**Olanzapine (N=248)**	**Placebo (N=118)**
Postural hypotension	5	2
Constipation	9	3
Weight gain	6	1
Dizziness	11	4
Personality disorder [a]	8	4
Akathisia	5	1

Personality disorder is the COSTART term for designating nonaggressive objectionable behavior. [a]

Table 10: Common Treatment-Emergent Adverse Reactions Associated with theUse of Oral Olanzapine in 3-Week and 4-Week Trials — Bipolar I Disorder (Manic or Mixed Episodes)

	Percentage of Patients Reporting Event	
Adverse Reaction	**Olanzapine (N=125)**	**Placebo (N=129)**
Asthenia	15	6
Dry Mouth	22	7
Constipation	11	5
Dyspepsia	11	5

Increased appetite	6	3
Somnolence	35	13
Dizziness	18	6
Tremor	6	3

— There was 1 adverse reaction (somnolence) observed at an incidence of 5% or greater among intramuscular olanzapine for injection-treated patients and not observed at an equivalent incidence among placebo-treated patients (olanzapine incidence at least twice that for placebo) during the placebo-controlled premarketing studies. The incidence of somnolence during the 24 hour IM treatment period in clinical trials in agitated patients with schizophrenia or bipolar I mania was 6% for intramuscular olanzapine for injection and 3% for placebo. *Olanzapine Intramuscular*

Adverse Reactions Occurring at an Incidence of 2% or More among Oral Olanzapine-Treated Patients in Short-Term,Placebo-Controlled Trials

enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred in 2% or more of patients treated with oral olanzapine (doses ≥2.5 mg/day) and with incidence greater than placebo who participated in the acute phase of placebo-controlled trials. **Table 11**

Table 11: Treatment-Emergent Adverse Reactions:Incidence in Short-Term, Placebo-Controlled Clinical Trials with Oral Olanzapine

	Percentage of Patients Reporting Event	
Body System/Adverse Reaction	**Olanzapine (N=532)**	**Placebo (N=294)**
Body as a Whole		
Accidental injury	12	8
Asthenia	10	9
Fever	6	2
Back pain	5	2
Chest pain	3	1
Cardiovascular System		
Postural hypotension	3	1
Tachycardia	3	1
Hypertension	2	1
Digestive System		
Dry mouth	9	5
Constipation	9	4
Dyspepsia	7	5
Vomiting	4	3
Increased appetite	3	2
Hemic and Lymphatic System		
Ecchymosis	5	3
Metabolic and Nutritional Disorders		
Weight gain	5	3
Peripheral edema	3	1
Musculoskeletal System		
Extremity pain (other than	5	3

joint)		
Joint pain	5	3
Nervous System		
Somnolence	29	13
Insomnia	12	11
Dizziness	11	4
Abnormal gait	6	1
Tremor	4	3
Akathisia	3	2
Hypertonia	3	2
Articulation impairment	2	1
Respiratory System		
Rhinitis	7	6
Cough increased	6	3
Pharyngitis	4	3
Special Senses		
Amblyopia	3	2
Urogenital System		
Urinary incontinence	2	1
Urinary tract infection	2	1

Commonly Observed Adverse Reactions in Short-Term Trials of Oral Olanzapine as Adjunct to Lithium or Valproate

In the bipolar I disorder (manic or mixed episodes) adjunct placebo-controlled trials, the most commonly observed adverse reactions associated with the combination of olanzapine and lithium or valproate (incidence of ≥5% and at least twice placebo) were:

Table 12: Common Treatment-Emergent Adverse Reactions Associated with theUse of Oral Olanzapine in 6-Week Adjunct to Lithium or Valproate Trials — Bipolar I Disorder (Manic or Mixed Episodes)

	Percentage of Patients Reporting Event	
Adverse Reaction	**Olanzapine with lithium or valproate (N=229)**	**Placebo with lithium or valproate (N=115)**
Dry mouth	32	9
Weight gain	26	7
Increased appetite	24	8
Dizziness	14	7
Back pain	8	4
Constipation	8	4
Speech disorder	7	1
Increased salivation	6	2
Amnesia	5	2
Paresthesia	5	2

Adverse Reactions Occurring at an Incidence of 2% or More among Oral Olanzapine-Treated Patients in Short-Term Trialsof Olanzapine as Adjunct to Lithium or Valproate

enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred in 2% or more of patients treated with the combination of olanzapine (doses ≥5 mg/day) and lithium or valproate and with incidence greater than lithium or valproate alone who participated in the acute phase of placebo-controlled combination trials. **Table 13**

Table 13: Treatment-Emergent Adverse Reactions: Incidence in Short-Term, Placebo-Controlled Clinical Trials ofOral Olanzapine as Adjunct to Lithium or Valproate

	Percentage of Patients Reporting Event	
Body System/Adverse Reaction	**Olanzapine with lithium or valproate (N=229)**	**Placebo with lithium or valproate (N=115)**
Body as a Whole		
Asthenia	18	13
Back pain	8	4
Accidental injury	4	2
Chest pain	3	2
Cardiovascular System		
Hypertension	2	1
Digestive System		
Dry mouth	32	9
Increased appetite	24	8
Thirst	10	6
Constipation	8	4
Increased salivation	6	2
Metabolic and Nutritional Disorders		
Weight gain	26	7
Peripheral edema	6	4
Edema	2	1
Nervous System		
Somnolence	52	27
Tremor	23	13
Depression	18	17
Dizziness	14	7
Speech Disorder	7	1
Amnesia	5	2
Paresthesia	5	2
Apathy	4	3
Confusion	4	1
Euphoria	3	2
Incoordination	2	0
Respiratory System		
Pharyngitis	4	1
Dyspnea	3	1

Skin and Appendages		
Sweating	3	1
Acne	2	0
Dry Skin	2	0
Special Senses		
Amblyopia	9	5
Abnormal vision	2	0
Urogenital System		
Dysmenorrhea [a]	2	0
Vaginitis [a]	2	0

Denominator used was for females only (olanzapine, N=128; placebo, N=51). [a]

For specific information about the adverse reactions observed with lithium or valproate, refer to the Adverse Reactions section of the package inserts for these other products.

Adverse Reactions Occurring at an Incidence of 1% or More among Intramuscular Olanzapine for Injection-Treated Patientsin Short-Term, Placebo-Controlled Trials

enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred in 1% or more of patients treated with intramuscular olanzapine for injection (dose range of 2.5 to 10 mg/injection) and with incidence greater than placebo who participated in the short-term, placebo-controlled trials in agitated patients with schizophrenia or bipolar I mania. **Table 14**

Table 14: Treatment-Emergent Adverse Reactions: Incidence in Short-Term (24 Hour), Placebo-Controlled Clinical Trialswith Intramuscular Olanzapine for Injection in Agitated Patients with Schizophrenia or Bipolar I Mania

	Percentage of Patients Reporting Event	
Body System/Adverse Reaction	**Olanzapine (N=415)**	**Placebo (N=150)**
Body as a Whole		
Asthenia	2	1
Cardiovascular System		
Hypotension	2	0
Postural hypotension	1	0
Nervous System		
Somnolence	6	3
Dizziness	4	2
Tremor	1	0

Additional Findings Observed in Clinical Trials

Dose Dependency of Adverse Reactions in Short-Term, Placebo-Controlled Trials

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by categorical analyses of formal rating scales during acute therapy in a controlled clinical trial comparing oral olanzapine at 3 fixed doses with placebo in the treatment of schizophrenia in a 6-week trial. *: Extrapyramidal Symptoms*

Table 15: Treatment-Emergent Extrapyramidal Symptoms Assessed by Rating Scales Incidencein a Fixed Dosage Range, Placebo-Controlled Clinical Trial of Oral Olanzapine in Schizophrenia — Acute Phase

	Percentage of Patients Reporting Event			
	Placebo	Olanzapine 5±2.5 mg/day	Olanzapine 10±2.5 mg/day	Olanzapine 15±2.5 mg/day
Parkinsonism [a]	15	14	12	14
Akathisia [b]	23	16	19	27

Percentage of patients with a Simpson-Angus Scale total score >3. [a]

Percentage of patients with a Barnes Akathisia Scale global score ≥2. [b]

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by spontaneously reported adverse reactions during acute therapy in the same controlled clinical trial comparing olanzapine at 3 fixed doses with placebo in the treatment of schizophrenia in a 6-week trial.

Table 16: Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Reactions Incidencein a Fixed Dosage Range, Placebo-Controlled Clinical Trial of Oral Olanzapine in Schizophrenia — Acute Phase

	Percentage of Patients Reporting Event			
	Placebo (N=68)	Olanzapine 5 ± 2.5 mg/day (N=65)	Olanzapine 10 ± 2.5 mg/day (N=64)	Olanzapine 15 ± 2.5 mg/day (N=69)
Dystonic events [a]	1	3	2	3
Parkinsonism events [b]	10	8	14	20
Akathisia events [c]	1	5	11	10
Dyskinetic events [d]	4	0	2	1
Residual events [e]	1	2	5	1
Any extrapyramidal event	16	15	25	32

Patients with the following COSTART terms were counted in this category: dystonia, generalized spasm, neck rigidity, oculogyric crisis, opisthotonos, torticollis. [a]

Patients with the following COSTART terms were counted in this category: akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor. [b]

Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia. [c]

Patients with the following COSTART terms were counted in this category: buccoglossal syndrome, choreoathetosis, dyskinesia, tardive dyskinesia. [d]

Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus, twitching. [e]

The following table enumerates the percentage of adolescent patients with treatment-emergent

extrapyramidal symptoms as assessed by spontaneously reported adverse reactions during acute therapy (dose range: 2.5 to 20 mg/day).

Table 17: Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Reactions Incidencein Placebo-Controlled Clinical Trials of Oral Olanzapine in Schizophrenia and Bipolar I Disorder — Adolescents

Categories [a]	Percentage of Patients Reporting Event	
	Placebo (N=89)	Olanzapine (N=179)
Dystonic events	0	1
Parkinsonism events	2	1
Akathisia events	4	6
Dyskinetic events	0	1
Nonspecific events	0	4
Any extrapyramidal event	6	10

Categories are based on Standard MedDRA Queries (SMQ) for extrapyramidal symptoms as defined in MedDRA version 12.0. [a]

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by categorical analyses of formal rating scales during controlled clinical trials comparing fixed doses of intramuscular olanzapine for injection with placebo in agitation. Patients in each dose group could receive up to 3 injections during the trials . Patient assessments were conducted during the 24 hours following the initial dose of intramuscular olanzapine for injection. *[see* **CLINICAL STUDIES ( ) 14.3***]*

Table 18: Treatment-Emergent Extrapyramidal Symptoms Assessed by Rating Scales Incidence in a Fixed Dose, Placebo-Controlled Clinical Trial of Intramuscular Olanzapine for Injection in Agitated Patients with Schizophrenia

	Percentage of Patients Reporting Event				
	Placebo	Olanzapine IM 2.5 mg	Olanzapine IM 5 mg	Olanzapine IM 7.5 mg	Olanzapine IM 10 mg
Parkinsonism [a]	0	0	0	0	3
Akathisia [b]	0	0	5	0	0

Percentage of patients with a Simpson-Angus Scale total score >3. [a]

Percentage of patients with a Barnes Akathisia Scale global score ≥2. [b]

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by spontaneously reported adverse reactions in the same controlled clinical trial comparing fixed doses of intramuscular Olanzapine for Injection with placebo in agitated patients with schizophrenia.

Table 19: Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Reactions

Incidence in a Fixed Dose, Placebo-Controlled Clinical Trial of Intramuscular Olanzapine for Injection in Agitated Patients with Schizophrenia

	Percentage of Patients Reporting Event				
	Placebo (N=45)	Olanzapine IM 2.5 mg (N=48)	Olanzapine IM 5 mg (N=45)	Olanzapine IM 7.5 mg (N=46)	Olanzapine IM 10 mg (N=46)
Dystonic events [a]	0	0	0	0	0
Parkinsonism events [b]	0	4	2	0	0
Akathisia events [c]	0	2	0	0	0
Dyskinetic events [d]	0	0	0	0	0
Residual events [e]	0	0	0	0	0
Any extrapyramidal events	0	4	2	0	0

Patients with the following COSTART terms were counted in this category: dystonia, generalized spasm, neck rigidity, oculogyric crisis, opisthotonos, torticollis. [a]

Patients with the following COSTART terms were counted in this category: akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor. [b]

Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia. [c]

Patients with the following COSTART terms were counted in this category: buccoglossal syndrome, choreoathetosis, dyskinesia, tardive dyskinesia. [d]

Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus, twitching. [e]

Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, the frequency and severity are greater with high potency and at higher doses of first generation antipsychotic drugs. In general, an elevated risk of acute dystonia may be observed in males and younger age groups receiving antipsychotics; however, events of dystonia have been reported infrequently (<1%) with olanzapine use. *: Dystonia, Class Effect*

The following table addresses dose relatedness for other adverse reactions using data from a schizophrenia trial involving fixed dosage ranges of oral olanzapine. It enumerates the percentage of patients with treatment-emergent adverse reactions for the 3 fixed-dose range groups and placebo. The data were analyzed using the Cochran-Armitage test, excluding the placebo group, and the table includes only those adverse reactions for which there was a trend. *: Other Adverse Reactions*

Table 20: Percentage of Patients from a Schizophrenia Trial with Treatment-Emergent Adverse Reactions for the 3 Dose Range Groups and Placebo

Adverse	Percentage of Patients Reporting Event

Reaction	Placebo (N=68)	Olanzapine 5 ± 2.5 mg/day (N=65)	Olanzapine 10 ± 2.5 mg/day (N=64)	Olanzapine 15 ± 2.5 mg/day (N=69)
Asthenia	15	8	9	20
Dry mouth	4	3	5	13
Nausea	9	0	2	9
Somnolence	16	20	30	39
Tremor	3	0	5	7

Differences among Fixed-Dose Groups Observed in Other Olanzapine Clinical Trials

In a single 8-week randomized, double-blind, fixed-dose study comparing 10 (N=199), 20 (N=200) and 40 (N=200) mg/day of oral olanzapine in patients with schizophrenia or schizoaffective disorder, differences among 3 dose groups were observed for the following safety outcomes: weight gain, prolactin elevation, fatigue and dizziness. Mean baseline to endpoint increase in weight (10 mg/day: 1.9 kg; 20 mg/day: 2.3 kg; 40 mg/day: 3 kg) was observed with significant differences between 10 vs 40 mg/day. Incidence of treatment-emergent prolactin elevation >24.2 ng/mL (female) or >18.77 ng/mL (male) at any time during the trial (10 mg/day: 31.2%; 20 mg/day: 42.7%; 40 mg/day: 61.1%) with significant differences between 10 vs 40 mg/day and 20 vs 40 mg/day; fatigue (10 mg/day: 1.5%; 20 mg/day: 2.1%; 40 mg/day: 6.6%) with significant differences between 10 vs 40 and 20 vs 40 mg/day; and dizziness (10 mg/day: 2.6%; 20 mg/day: 1.6%; 40 mg/day: 6.6%) with significant differences between 20 vs 40 mg, was observed.

Other Adverse Reactions Observed During the Clinical Trial Evaluation of Oral Olanzapine

Following is a list of treatment-emergent adverse reactions reported by patients treated with oral olanzapine (at multiple doses ≥1 mg/day) in clinical trials. This listing is not intended to include reactions (1) already listed in previous tables or elsewhere in labeling, (2) for which a drug cause was remote, (3) which were so general as to be uninformative, (4) which were not considered to have significant clinical implications, or (5) which occurred at a rate equal to or less than placebo. Reactions are classified by body system using the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients; rare reactions are those occurring in fewer than 1/1000 patients.

— chills, face edema, photosensitivity reaction, suicide attempt ; chills and fever, hangover effect, sudden death . **Body as a Whole***Infrequent:*[1]*Rare:*[1]

— cerebrovascular accident, vasodilatation. **Cardiovascular System***Infrequent:*

— nausea and vomiting, tongue edema; ileus, intestinal obstruction, liver fatty deposit. **Digestive System***Infrequent:Rare:*

— leukopenia, thrombocytopenia. **Hemic and Lymphatic System***Infrequent:*

— alkaline phosphatase increased, bilirubinemia, hypoproteinemia. **Metabolic and Nutritional Disorders***Infrequent:*

— osteoporosis. **Musculoskeletal System***Rare:*

— ataxia, dysarthria, libido decreased, stupor; coma. **Nervous System***Infrequent:Rare:*

— epistaxis; lung edema. **Respiratory System***Infrequent:Rare:*

— alopecia. **Skin and Appendages***Infrequent:*

— abnormality of accommodation, dry eyes; mydriasis. **Special Senses***Infrequent:Rare:*

— amenorrhea , breast pain, decreased menstruation, impotence , increased menstruation , menorrhagia ,

metrorrhagia , polyuria , urinary frequency, urinary retention, urinary urgency, urination impaired. **Urogenital System***Infrequent:*[222222]

These terms represent serious adverse events but do not meet the definition for adverse drug reactions. They are included here because of their seriousness. [1]

Adjusted for gender. [2]

Other Adverse Reactions Observed During the Clinical Trial Evaluation of Intramuscular Olanzapine for Injection

Following is a list of treatment-emergent adverse reactions reported by patients treated with intramuscular Olanzapine for Injection (at 1 or more doses ≥2.5 mg/injection) in clinical trials. This listing is not intended to include reactions (1) already listed in previous tables or elsewhere in labeling, (2) for which a drug cause was remote, (3) which were so general as to be uninformative, (4) which were not considered to have significant clinical implications, or (5) for which occurred at a rate equal to or less than placebo. Reactions are classified by body system using the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients.

— injection site pain. **Body as a Whole***Frequent:*

— syncope. **Cardiovascular System***Infrequent:*

— nausea. **Digestive System***Infrequent:*

— creatine phosphokinase increased. **Metabolic and Nutritional Disorders***Infrequent:*

Clinical Trials in Adolescent Patients (age 13 to 17 years)

Commonly Observed Adverse Reactions in Oral Olanzapine Short-Term, Placebo-Controlled Trials

Adverse reactions in adolescent patients treated with oral olanzapine (doses ≥2.5 mg) reported with an incidence of 5% or more and reported at least twice as frequently as placebo-treated patients are listed in . **Table 21**

Table 21: Treatment-Emergent Adverse Reactions of ≥5% Incidence among Adolescents (13 to 17 Years Old) with Schizophrenia or Bipolar I Disorder (Manic or Mixed Episodes)

Adverse Reactions Adverse Reactions	**Percentage of Patients Reporting Event**			
	6 Week Trial % Schizophrenia Patients		**3 Week Trial % Bipolar Patients**	
	Olanzapine (N=72)	**Placebo (N=35)**	**Olanzapine (N=107)**	**Placebo (N=54)**
Sedation [a]	39	9	48	9
Weight increased	31	9	29	4
Headache	17	6	17	17
Increased appetite	17	9	29	4
Dizziness	8	3	7	2
Abdominal pain [b]	6	3	6	7
Pain in extremity	6	3	5	0
Fatigue	3	3	14	6
Dry mouth	4	0	7	0

Patients with the following MedDRA terms were counted in this category: hypersomnia, lethargy, sedation, somnolence. [a]

Patients with the following MedDRA terms were counted in this category: abdominal pain, abdominal pain lower, abdominal pain upper. [b]

Adverse Reactions Occurring at an Incidence of 2% or More among Oral Olanzapine-Treated Patients in Short-Term (3 to 6weeks), Placebo-Controlled Trials

Adverse reactions in adolescent patients treated with oral olanzapine (doses ≥2.5 mg) reported with an incidence of 2% or more and greater than placebo are listed in . **Table 22**

≥ Table 22: Treatment-Emergent Adverse Reactions of2% Incidence among Adolescents (13 to 17 Years Old) (Combined Incidence from Short-Term, Placebo-Controlled Clinical Trials of Schizophreniaor Bipolar I Disorder [Manic or Mixed Episodes])

	Percentage of Patients Reporting Event	
Adverse Reaction	**Olanzapine (N=179)**	**Placebo (N=89)**
Sedation [a]	44	9
Weight increased	30	6
Increased appetite	24	6
Headache	17	12
Fatigue	9	4
Dizziness	7	2
Dry mouth	6	0
Pain in extremity	5	1
Constipation	4	0
Nasopharyngitis	4	2
Diarrhea	3	0
Restlessness	3	2
Liver enzymes increased [b]	8	1
Dyspepsia	3	1
Epistaxis	3	0
Respiratory tract infection [c]	3	2
Sinusitis	3	0
Arthralgia	2	0
Musculoskeletal stiffness	2	0

Patients with the following MedDRA terms were counted in this category: hypersomnia, lethargy, sedation, somnolence. [a]

The terms alanine aminotransferase (ALT), aspartate aminotransferase (AST), and hepatic enzyme were combined under liver enzymes. [b]

Patients with the following MedDRA terms were counted in this category: lower respiratory tract infection, respiratory tract infection, respiratory tract infection viral, upper respiratory tract infection, viral upper respiratory tract infection. [c]

6.2 Vital Signs and Laboratory Studies

Vital Sign Changes

Oral olanzapine was associated with orthostatic hypotension and tachycardia in clinical trials. Intramuscular olanzapine for injection was associated with bradycardia, hypotension, and tachycardia in clinical trials . *[see* **WARNINGS AND PRECAUTIONS ( ) 5***]*

Laboratory Changes

An assessment of the premarketing experience for olanzapine revealed an association with asymptomatic increases in ALT, AST, and GGT. Within the original premarketing database of about 2400 adult patients with baseline ALT ≤90 IU/L, the incidence of ALT elevations to >200 IU/L was 2% (50/2381). None of these patients experienced jaundice or other symptoms attributable to liver impairment and most had transient changes that tended to normalize while olanzapine treatment was continued. *Olanzapine Monotherapy in Adults:*

In placebo-controlled olanzapine monotherapy studies in adults, clinically significant ALT elevations (change from <3 times the upper limit of normal [ULN] at baseline to ≥3 times ULN) were observed in 5% (77/1426) of patients exposed to olanzapine compared to 1% (10/1187) of patients exposed to placebo. ALT elevations ≥5 times ULN were observed in 2% (29/1438) of olanzapine-treated patients, compared to 0.3% (4/1196) of placebo-treated patients. ALT values returned to normal, or were decreasing, at last follow-up in the majority of patients who either continued treatment with olanzapine or discontinued olanzapine. No patient with elevated ALT values experienced jaundice, liver failure, or met the criteria for Hy's Rule.

Rare postmarketing reports of hepatitis have been received. Very rare cases of cholestatic or mixed liver injury have also been reported in the postmarketing period.

Caution should be exercised in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic drugs.

Olanzapine administration was also associated with increases in serum prolactin , with an asymptomatic elevation of the eosinophil count in 0.3% of patients, and with an increase in CPK. *[see* **WARNINGS AND PRECAUTIONS ( ) 5.15***]*

In placebo-controlled clinical trials of adolescent patients with schizophrenia or bipolar I disorder (manic or mixed episodes), greater frequencies for the following treatment-emergent findings, at anytime, were observed in laboratory analytes compared to placebo: elevated ALT (≥3X ULN in patients with ALT at baseline <3X ULN), (12% vs 2%); elevated AST (28% vs 4%); low total bilirubin (22% vs 7%); elevated GGT (10% vs 1%); and elevated prolactin (47% vs 7%). ***Olanzapine Monotherapy in Adolescents****:*

In placebo-controlled olanzapine monotherapy studies in adolescents, clinically significant ALT elevations (change from <3 times ULN at baseline to ≥3 times ULN) were observed in 12% (22/192) of patients exposed to olanzapine compared to 2% (2/109) of patients exposed to placebo. ALT elevations ≥5 times ULN were observed in 4% (8/192) of olanzapine-treated patients, compared to 1% (1/109) of placebo-treated patients. ALT values returned to normal, or were decreasing, at last follow-up in the majority of patients who either continued treatment with olanzapine or discontinued olanzapine. No adolescent patient with elevated ALT values experienced jaundice, liver failure, or met the criteria for Hy's Rule.

ECG Changes

In pooled studies of adults as well as pooled studies of adolescents, there were no significant differences between olanzapine and placebo in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc (Fridericia corrected), and PR intervals. Olanzapine use was associated with a mean increase in heart rate compared to placebo (adults: +2.4 beats per minute vs no change with placebo; adolescents: +6.3 beats per minute vs -5.1 beats per minute with placebo). This increase in heart rate may be related to olanzapine's potential for inducing

orthostatic changes . *[see***WARNINGS AND PRECAUTIONS ( ) 5.8***]*

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Olanzapine for Injection. Because these reactions are reported voluntarily from a population of uncertain size, it is difficult to reliably estimate their frequency or evaluate a causal relationship to drug exposure.

Adverse reactions reported since market introduction that were temporally (but not necessarily causally) related to Olanzapine for Injection therapy include the following: allergic reaction (e.g., anaphylactoid reaction, angioedema, pruritus or urticaria), diabetic coma, diabetic ketoacidosis, discontinuation reaction (diaphoresis, nausea or vomiting), jaundice, neutropenia, pancreatitis, priapism, rash, rhabdomyolysis, and venous thromboembolic events (including pulmonary embolism and deep venous thrombosis). Random cholesterol levels of ≥240 mg/dL and random triglyceride levels of ≥1000 mg/dL have been reported.

7 DRUG INTERACTIONS

The risks of using olanzapine in combination with other drugs have not been extensively evaluated in systematic studies.

7.1 Potential for Other Drugs to Affect Olanzapine

Diazepam

The co-administration of diazepam with olanzapine potentiated the orthostatic hypotension observed with olanzapine . *[see* **DRUG INTERACTIONS ( ) 7.2***]*

Cimetidine and Antacids

Single doses of cimetidine (800 mg) or aluminum- and magnesium-containing antacids did not affect the oral bioavailability of olanzapine.

Inducers of CYP1A2

Carbamazepine therapy (200 mg bid) causes an approximately 50% increase in the clearance of olanzapine. This increase is likely due to the fact that carbamazepine is a potent inducer of CYP1A2 activity. Higher daily doses of carbamazepine may cause an even greater increase in olanzapine clearance.

Alcohol

Ethanol (45 mg/70 kg single dose) did not have an effect on olanzapine pharmacokinetics. The co-administration of alcohol (i.e., ethanol) with olanzapine potentiated the orthostatic hypotension observed with olanzapine . *[see* **DRUG INTERACTIONS ( ) 7.2***]*

Inhibitors of CYP1A2

Fluvoxamine, a CYP1A2 inhibitor, decreases the clearance of olanzapine. This results in a mean increase in olanzapine C following fluvoxamine of 54% in female nonsmokers and 77% in male smokers. The mean increase in olanzapine AUC is 52% and 108%, respectively. Lower doses of olanzapine should be considered in patients receiving concomitant treatment with fluvoxamine. *Fluvoxamine:*$_{\max}$

Warfarin

Warfarin (20 mg single dose) did not affect olanzapine pharmacokinetics . *[see* **DRUG INTERACTIONS ( ) 7.2***]*

Inducers of CYP1A2 or Glucuronyl Transferase

Omeprazole and rifampin may cause an increase in olanzapine clearance.

Charcoal

The administration of activated charcoal (1 g) reduced the C and AUC of oral olanzapine by about 60%. As peak olanzapine levels are not typically obtained until about 6 hours after dosing, charcoal may be a useful treatment for olanzapine overdose. $_{max}$

7.2 Potential for Olanzapine to Affect Other Drugs

CNS Acting Drugs

Given the primary CNS effects of olanzapine, caution should be used when olanzapine is taken in combination with other centrally acting drugs and alcohol.

Antihypertensive Agents

Olanzapine, because of its potential for inducing hypotension, may enhance the effects of certain antihypertensive agents.

Levodopa and Dopamine Agonists

Olanzapine may antagonize the effects of levodopa and dopamine agonists.

Lorazepam (IM)

Administration of intramuscular lorazepam (2 mg) 1 hour after intramuscular Olanzapine for Injection (5 mg) did not significantly affect the pharmacokinetics of olanzapine, unconjugated lorazepam, or total lorazepam. However, this co-administration of intramuscular lorazepam and intramuscular Olanzapine for Injection added to the somnolence observed with either drug alone . *[see* **WARNINGS AND PRECAUTIONS ( ) 5.8***]*

Lithium

Multiple doses of olanzapine (10 mg for 8 days) did not influence the kinetics of lithium. Therefore, concomitant olanzapine administration does not require dosage adjustment of lithium . *[see***WARNINGS AND PRECAUTIONS ( ) 5.16***]*

Valproate

Olanzapine (10 mg daily for 2 weeks) did not affect the steady state plasma concentrations of valproate. Therefore, concomitant olanzapine administration does not require dosage adjustment of valproate. . *[see* **WARNINGS AND PRECAUTIONS ( ) 5.16***]*

Effect of Olanzapine on Drug Metabolizing Enzymes

studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by these enzymes. *In vitro*

Imipramine

Single doses of olanzapine did not affect the pharmacokinetics of imipramine or its active metabolite desipramine.

Warfarin

Single doses of olanzapine did not affect the pharmacokinetics of warfarin . *[see* **DRUG INTERACTIONS ( ) 7.1***]*

Diazepam

Olanzapine did not influence the pharmacokinetics of diazepam or its active metabolite N-desmethyldiazepam. However, diazepam co-administered with olanzapine increased the orthostatic hypotension observed with either drug given alone . *[see* **DRUG INTERACTIONS ( ) 7.1***]*

Alcohol

Multiple doses of olanzapine did not influence the kinetics of ethanol . *[see* **DRUG INTERACTIONS (7.1)***]*

Biperiden

Multiple doses of olanzapine did not influence the kinetics of biperiden.

Theophylline

Multiple doses of olanzapine did not affect the pharmacokinetics of theophylline or its metabolites.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects, Pregnancy Category C

In oral reproduction studies in rats at doses up to 18 mg/kg/day and in rabbits at doses up to 30 mg/kg/day (9 and 30 times the maximum recommended human daily oral dose on a mg/m basis, respectively) no evidence of teratogenicity was observed. In an oral rat teratology study, early resorptions and increased numbers of nonviable fetuses were observed at a dose of 18 mg/kg/day (9 times the maximum recommended human daily oral dose on a mg/m basis). Gestation was prolonged at 10 mg/kg/day (5 times the maximum recommended human daily oral dose on a mg/m basis). In an oral rabbit teratology study, fetal toxicity (manifested as increased resorptions and decreased fetal weight) occurred at a maternally toxic dose of 30 mg/kg/day (30 times the maximum recommended human daily oral dose on a mg/m basis). Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. [2222]

Placental transfer of olanzapine occurs in rat pups.

There are no adequate and well-controlled trials with olanzapine in pregnant females. Seven pregnancies were observed during clinical trials with olanzapine, including 2 resulting in normal births, 1 resulting in neonatal death due to a cardiovascular defect, 3 therapeutic abortions, and 1 spontaneous abortion.

Non-Teratogenic Effects

Neonates exposed to antipsychotic drugs (including Olanzapine for Injection), during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

Olanzapine for Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.2 Labor and Delivery

The effect of olanzapine on labor and delivery in humans is unknown. Parturition in rats was not affected by olanzapine.

8.3 Nursing Mothers

In a study in lactating, healthy women, olanzapine was excreted in breast milk. Mean infant dose at steady state was estimated to be 1.8% of the maternal olanzapine dose. It is recommended that women receiving olanzapine should not breast-feed.

8.4 Pediatric Use

Compared to patients from adult clinical trials, adolescents were likely to gain more weight, experience increased sedation, and have greater increases in total cholesterol, triglycerides, LDL cholesterol, prolactin and hepatic aminotransferase levels AND . When deciding among the alternative treatments available for adolescents, clinicians should consider the increased potential (in adolescents as compared with adults) for weight gain and hyperlipidemia. Clinicians should consider the potential long-term risks when prescribing to adolescents, and in many cases this may lead them to consider prescribing other drugs first in adolescents. *[see* **WARNINGS AND PRECAUTIONS (, , ,) 5.55.65.155.17ADVERSE REACTIONS ( ) 6.2***]*

Safety and effectiveness of olanzapine for injection in children <18 years of age have not been established . *[see* **PATIENT COUNSELING INFORMATION ( ) 17.13***]*

8.5 Geriatric Use

Studies in elderly patients with dementia-related psychosis have suggested that there may be a different tolerability profile in this population compared to younger patients with schizophrenia. Elderly patients with dementia-related psychosis treated with olanzapine are at an increased risk of death compared to placebo. In placebo-controlled studies of olanzapine in elderly patients with dementia related psychosis, there was a higher incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) in patients treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis. Also, the presence of factors that might decrease pharmacokinetic clearance or increase the pharmacodynamic response to olanzapine should lead to consideration of a lower starting dose for any geriatric patient AND . *[see* **BOXED WARNINGWARNINGS AND PRECAUTIONS ( ) 5.1***]*

9 DRUG ABUSE AND DEPENDENCE

9.3 Dependence

In studies prospectively designed to assess abuse and dependence potential, olanzapine was shown to have acute depressive CNS effects but little or no potential of abuse or physical dependence in rats administered oral doses up to 15 times the maximum recommended human daily oral dose (20 mg) and rhesus monkeys administered oral doses up to 8 times the maximum recommended human daily oral dose on a mg/m basis. ^{2}

Olanzapine has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic, and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of olanzapine (e.g., development of tolerance, increases in dose, drug-seeking behavior).

10 OVERDOSAGE

10.1 Human Experience

In premarketing trials involving more than 3100 patients and/or normal subjects, accidental or intentional acute overdosage of olanzapine was identified in 67 patients. In the patient taking the largest identified amount, 300 mg, the only symptoms reported were drowsiness and slurred speech. In the limited number of patients who were evaluated in hospitals, including the patient taking 300 mg, there were no observations indicating an adverse change in laboratory analytes or ECG. Vital signs were usually within normal limits following overdoses.

In postmarketing reports of overdose with olanzapine alone, symptoms have been reported in the majority of cases. In symptomatic patients, symptoms with ≥10% incidence included

agitation/aggressiveness, dysarthria, tachycardia, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma. Among less commonly reported symptoms were the following potentially medically serious reactions: aspiration, cardiopulmonary arrest, cardiac arrhythmias (such as supraventricular tachycardia and 1 patient experiencing sinus pause with spontaneous resumption of normal rhythm), delirium, possible neuroleptic malignant syndrome, respiratory depression/arrest, convulsion, hypertension, and hypotension. Company has received reports of fatality in association with overdose of olanzapine alone. In 1 case of death, the amount of acutely ingested olanzapine was reported to be possibly as low as 450 mg of oral olanzapine; however, in another case, a patient was reported to survive an acute olanzapine ingestion of approximately 2 g of oral olanzapine.

10.2 Management of Overdose

The possibility of multiple drug involvement should be considered. In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation, which may include intubation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The administration of activated charcoal (1 g) reduced the C and AUC of oral olanzapine by about 60%. As peak olanzapine levels are not typically obtained until about 6 hours after dosing, charcoal may be a useful treatment for olanzapine overdose.

max

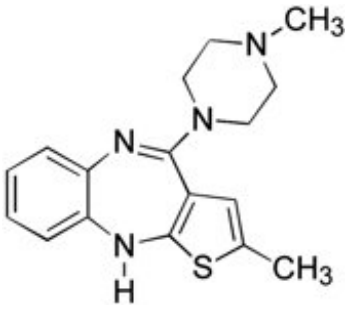
The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

There is no specific antidote to olanzapine. Therefore, appropriate supportive measures should be initiated. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. (Do not use epinephrine, dopamine, or other sympathomimetics with beta-agonist activity, since beta stimulation may worsen hypotension in the setting of olanzapine-induced alpha blockade.) Close medical supervision and monitoring should continue until the patient recovers.

For specific information about overdosage with lithium or valproate, refer to the overdosage section of the package inserts for these products.

11 DESCRIPTION

Olanzapine is an atypical antipsychotic that belongs to the thienobenzodiazepine class. The chemical designation is 2-methyl-4-(4-methyl-1-piperazinyl)-10 -thieno[2,3-] [1,5]benzodiazepine. The molecular formula is C H N S, which corresponds to a molecular weight of 312.44. The chemical structure is: Hb_{17204}



Olanzapine is a yellow crystalline solid, which is practically insoluble in water.

Olanzapine for Injection is intended for intramuscular use only.

Each vial provides for the administration of 10 mg (32 µmol) olanzapine with inactive ingredients 50 mg lactose monohydrate and 3.5 mg tartaric acid. Hydrochloric acid and/or sodium hydroxide may have been added during manufacturing to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of olanzapine, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine and serotonin type 2 (5HT) antagonism. The mechanism of action of olanzapine in the treatment of acute manic or mixed episodes associated with bipolar I disorder is unknown. $_{2}$

12.2 Pharmacodynamics

Olanzapine binds with high affinity to the following receptors: serotonin 5HT , 5HT (K =4, 11, and 5 nM, respectively), dopamine D (K =11-31 nM), histamine H (K =7 nM), and adrenergic α receptors (K =19 nM). Olanzapine is an antagonist with moderate affinity binding for serotonin 5HT (K =57 nM) and muscarinic M (K =73, 96, 132, 32, and 48 nM, respectively). Olanzapine binds weakly to GABA , BZD, and β-adrenergic receptors (K >10 µM). $_{2A/2C6i1-4i1i1i3i1-5iAi}$

Antagonism at receptors other than dopamine and 5HT may explain some of the other therapeutic and side effects of olanzapine. Olanzapine's antagonism of muscarinic M receptors may explain its anticholinergic-like effects. Olanzapine's antagonism of histamine H receptors may explain the somnolence observed with this drug. Olanzapine's antagonism of adrenergic α receptors may explain the orthostatic hypotension observed with this drug. $_{21-511}$

12.3 Pharmacokinetics

Oral Administration, Monotherapy

Olanzapine is well absorbed and reaches peak concentrations in approximately 6 hours following an oral dose. It is eliminated extensively by first pass metabolism, with approximately 40% of the dose metabolized before reaching the systemic circulation. Food does not affect the rate or extent of olanzapine absorption. Pharmacokinetic studies showed that olanzapine tablets and olanzapine orally disintegrating tablets dosage forms of olanzapine are bioequivalent.

Olanzapine displays linear kinetics over the clinical dosing range. Its half-life ranges from 21 to 54 hours (5th to 95th percentile; mean of 30 hr), and apparent plasma clearance ranges from 12 to 47 L/hr (5th to 95th percentile; mean of 25 L/hr).

Administration of olanzapine once daily leads to steady-state concentrations in about 1 week that are approximately twice the concentrations after single doses. Plasma concentrations, half-life, and clearance of olanzapine may vary between individuals on the basis of smoking status, gender, and age.

Olanzapine is extensively distributed throughout the body, with a volume of distribution of approximately 1000 L. It is 93% bound to plasma proteins over the concentration range of 7 to 1100 ng/mL, binding primarily to albumin and α -acid glycoprotein. $_{1}$

Metabolism and Elimination

Following a single oral dose of C labeled olanzapine, 7% of the dose of olanzapine was recovered in the urine as unchanged drug, indicating that olanzapine is highly metabolized. Approximately 57% and 30% of the dose was recovered in the urine and feces, respectively. In the plasma, olanzapine accounted for only 12% of the AUC for total radioactivity, indicating significant exposure to metabolites. After multiple dosing, the major circulating metabolites were the 10-N-glucuronide, present at steady state at

44% of the concentration of olanzapine, and 4´-N-desmethyl olanzapine, present at steady state at 31% of the concentration of olanzapine. Both metabolites lack pharmacological activity at the concentrations observed. [14]

Direct glucuronidation and cytochrome P450 (CYP) mediated oxidation are the primary metabolic pathways for olanzapine. studies suggest that CYPs 1A2 and 2D6, and the flavin-containing monooxygenase system are involved in olanzapine oxidation. CYP2D6 mediated oxidation appears to be a minor metabolic pathway , because the clearance of olanzapine is not reduced in subjects who are deficient in this enzyme *In vitroin vivo*

Intramuscular Administration

Olanzapine for Injection results in rapid absorption with peak plasma concentrations occurring within 15 to 45 minutes. Based upon a pharmacokinetic study in healthy volunteers, a 5 mg dose of intramuscular Olanzapine for Injection produces, on average, a maximum plasma concentration approximately 5 times higher than the maximum plasma concentration produced by a 5 mg dose of oral olanzapine. Area under the curve achieved after an intramuscular dose is similar to that achieved after oral administration of the same dose. The half-life observed after intramuscular administration is similar to that observed after oral dosing. The pharmacokinetics are linear over the clinical dosing range. Metabolic profiles after intramuscular administration are qualitatively similar to metabolic profiles after oral administration.

Specific Populations

Renal Impairment

Because olanzapine is highly metabolized before excretion and only 7% of the drug is excreted unchanged, renal dysfunction alone is unlikely to have a major impact on the pharmacokinetics of olanzapine. The pharmacokinetic characteristics of olanzapine were similar in patients with severe renal impairment and normal subjects, indicating that dosage adjustment based upon the degree of renal impairment is not required. In addition, olanzapine is not removed by dialysis. The effect of renal impairment on metabolite elimination has not been studied.

Hepatic Impairment

Although the presence of hepatic impairment may be expected to reduce the clearance of olanzapine, a study of the effect of impaired liver function in subjects (n=6) with clinically significant (Childs Pugh Classification A and B) cirrhosis revealed little effect on the pharmacokinetics of olanzapine.

Geriatric

In a study involving 24 healthy subjects, the mean elimination half-life of olanzapine was about 1.5 times greater in elderly (≥65 years) than in nonelderly subjects (<65 years). Caution should be used in dosing the elderly, especially if there are other factors that might additively influence drug metabolism and/or pharmacodynamic sensitivity . *[see* **DOSAGE AND ADMINISTRATION ( ) 2***]*

Gender

Clearance of olanzapine is approximately 30% lower in women than in men. There were, however, no apparent differences between men and women in effectiveness or adverse effects. Dosage modifications based on gender should not be needed.

Smoking Status

Olanzapine clearance is about 40% higher in smokers than in nonsmokers, although dosage modifications are not routinely recommended.

Race

studies have shown that exposures are similar among Japanese, Chinese and Caucasians, especially after normalization for body weight differences. Dosage modifications for race are, therefore, not recommended. *In vivo*

Combined Effects

The combined effects of age, smoking, and gender could lead to substantial pharmacokinetic differences in populations. The clearance in young smoking males, for example, may be 3 times higher than that in elderly nonsmoking females. Dosing modification may be necessary in patients who exhibit a combination of factors that may result in slower metabolism of olanzapine . *[see* **DOSAGE AND ADMINISTRATION ( ) 2***]*

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Oral carcinogenicity studies were conducted in mice and rats. Olanzapine was administered to mice in two 78-week studies at doses of 3, 10, 30/20 mg/kg/day (equivalent to 0.8 to 5 times the maximum recommended human daily oral dose on a mg/m basis) and 0.25, 2, 8 mg/kg/day (equivalent to 0.06 to 2 times the maximum recommended human daily oral dose on a mg/m basis). Rats were dosed for 2 years at doses of 0.25, 1, 2.5, 4 mg/kg/day (males) and 0.25, 1, 4, 8 mg/kg/day (females) (equivalent to 0.13 to 2 and 0.13 to 4 times the maximum recommended human daily oral dose on a mg/m basis, respectively). The incidence of liver hemangiomas and hemangiosarcomas was significantly increased in 1 mouse study in female mice dosed at 8 mg/kg/day (2 times the maximum recommended human daily oral dose on a mg/m basis). These tumors were not increased in another mouse study in females dosed at 10 or 30/20 mg/kg/day (2 to 5 times the maximum recommended human daily oral dose on a mg/m basis); in this study, there was a high incidence of early mortalities in males of the 30/20 mg/kg/day group. The incidence of mammary gland adenomas and adenocarcinomas was significantly increased in female mice dosed at ≥2 mg/kg/day and in female rats dosed at ≥4 mg/kg/day (0.5 and 2 times the maximum recommended human daily oral dose on a mg/m basis, respectively). Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the olanzapine carcinogenicity studies; however, measurements during subchronic toxicity studies showed that olanzapine elevated serum prolactin levels up to 4-fold in rats at the same doses used in the carcinogenicity study. An increase in mammary gland neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin mediated. The relevance for human risk of the finding of prolactin mediated endocrine tumors in rodents is unknown . [222222]*[see* **WARNINGS AND PRECAUTIONS ( ) 5.15***]*

Mutagenesis

No evidence of genotoxic potential for olanzapine was found in the Ames reverse mutation test, micronucleus test in mice, the chromosomal aberration test in Chinese hamster ovary cells, unscheduled DNA synthesis test in rat hepatocytes, induction of forward mutation test in mouse lymphoma cells, or sister chromatid exchange test in bone marrow of Chinese hamsters. *in vivoin vivo*

Impairment of Fertility

In an oral fertility and reproductive performance study in rats, male mating performance, but not fertility, was impaired at a dose of 22.4 mg/kg/day and female fertility was decreased at a dose of 3 mg/kg/day (11 and 1.5 times the maximum recommended human daily oral dose on a mg/m basis, respectively). Discontinuance of olanzapine treatment reversed the effects on male mating performance. In female rats, the precoital period was increased and the mating index reduced at 5 mg/kg/day (2.5 times the maximum recommended human daily oral dose on a mg/m basis). Diestrous was prolonged and estrous delayed at 1.1 mg/kg/day (0.6 times the maximum recommended human daily oral dose on a mg/m basis); therefore olanzapine may produce a delay in ovulation. [222]

13.2 Animal Toxicology and/or Pharmacology

In animal studies with olanzapine, the principal hematologic findings were reversible peripheral

cytopenias in individual dogs dosed at 10 mg/kg (17 times the maximum recommended human daily oral dose on a mg/m basis), dose-related decreases in lymphocytes and neutrophils in mice, and lymphopenia in rats. A few dogs treated with 10 mg/kg developed reversible neutropenia and/or reversible hemolytic anemia between 1 and 10 months of treatment. Dose-related decreases in lymphocytes and neutrophils were seen in mice given doses of 10 mg/kg (equal to 2 times the maximum recommended human daily oral dose on a mg/m basis) in studies of 3 months' duration. Nonspecific lymphopenia, consistent with decreased body weight gain, occurred in rats receiving 22.5 mg/kg (11 times the maximum recommended human daily oral dose on a mg/m basis) for 3 months or 16 mg/kg (8 times the maximum recommended human daily oral dose on a mg/m basis) for 6 or 12 months. No evidence of bone marrow cytotoxicity was found in any of the species examined. Bone marrows were normocellular or hypercellular, indicating that the reductions in circulating blood cells were probably due to peripheral (non-marrow) factors. [2222]

14 CLINICAL STUDIES

14.3 Agitation Associated with Schizophrenia and Bipolar I Mania

The efficacy of intramuscular Olanzapine for Injection for the treatment of agitation was established in 3 short-term (24 hours of IM treatment) placebo-controlled trials in agitated adult inpatients from 2 diagnostic groups: schizophrenia and bipolar I disorder (manic or mixed episodes). Each of the trials included a single active comparator treatment arm of either haloperidol injection (schizophrenia studies) or lorazepam injection (bipolar I mania study). Patients enrolled in the trials needed to be: (1) judged by the clinical investigators as clinically agitated and clinically appropriate candidates for treatment with intramuscular medication, and (2) exhibiting a level of agitation that met or exceeded a threshold score of ≥14 on the 5 items comprising the Positive and Negative Syndrome Scale (PANSS) Excited Component (i.e., poor impulse control, tension, hostility, uncooperativeness and excitement items) with at least 1 individual item score ≥4 using a 1 to 7 scoring system (1=absent, 4=moderate, 7=extreme). In the studies, the mean baseline PANSS Excited Component score was 18.4, with scores ranging from 13 to 32 (out of a maximum score of 35), thus suggesting predominantly moderate levels of agitation with some patients experiencing mild or severe levels of agitation. The primary efficacy measure used for assessing agitation signs and symptoms in these trials was the change from baseline in the PANSS Excited Component at 2 hours post-injection. Patients could receive up to 3 injections during the 24 hour IM treatment periods; however, patients could not receive the second injection until after the initial 2 hour period when the primary efficacy measure was assessed. The results of the trials follow:

(1) In a placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for schizophrenia (n=270), 4 fixed intramuscular Olanzapine for Injection doses of 2.5 mg, 5 mg, 7.5 mg and 10 mg were evaluated. All doses were statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection. However, the effect was larger and more consistent for the 3 highest doses. There were no significant pairwise differences for the 7.5 and 10 mg doses over the 5 mg dose.

(2) In a second placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for schizophrenia (n=311), 1 fixed intramuscular Olanzapine for Injection dose of 10 mg was evaluated. Olanzapine for Injection was statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection.

(3) In a placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for bipolar I disorder (and currently displaying an acute manic or mixed episode with or without psychotic features) (n=201), 1 fixed intramuscular Olanzapine for Injection dose of 10 mg was evaluated. Olanzapine for Injection was statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection.

Examination of population subsets (age, race, and gender) did not reveal any differential responsiveness on the basis of these subgroupings.

16 HOW SUPPLIED/STORAGE AND HANDLING

NDC:64725-3159-1 in a VIAL of 10 INJECTION, POWDER, FOR SOLUTIONS

16.1 How Supplied

Olanzapine for Injection is available in:

NDC 0781-3159-72, 10 mg vial (1s)

NDC 0781-3159-95, package of 10 vials

16.2 Storage and Handling

Store Olanzapine for Injection vials (before reconstitution) at controlled room temperature, 20° to 25°C (68° to 77°F) [USP Controlled Room Temperature]. Reconstituted Olanzapine for Injection may be stored at controlled room temperature, 20° to 25°C (68° to 77°F) [USP Controlled Room Temperature] for up to 1 hour if necessary. The USP defines controlled room temperature as a temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25°C (68° to 77°F); that results in a mean kinetic temperature calculated to be not more than 25°C; and that allows for excursions between 15° and 30°C (59° and 86°F) that are experienced in pharmacies, hospitals, and warehouses. *seeseeDiscard any unused portion of reconstituted Olanzapine for InjectionIntraMuscular.*

Protect Olanzapine for Injection from light, do not freeze.

17 PATIENT COUNSELING INFORMATION

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Olanzapine for Injection as monotherapy. If you do not think you are getting better or have any concerns about your condition while taking Olanzapine for Injection, call your doctor.

17.2 Elderly Patients with Dementia-Related Psychosis: Increased Mortality and Cerebrovascular Adverse Events (CVAE), Including Stroke

Patients and caregivers should be advised that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Patients and caregivers should be advised that elderly patients with dementia-related psychosis treated with Olanzapine for Injection had a significantly higher incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) compared with placebo.

Olanzapine for Injection is not approved for elderly patients with dementia-related psychosis AND . *[see* **BOXED WARNINGWARNINGS AND PRECAUTIONS ( ) 5.1***]*

17.3 Neuroleptic Malignant Syndrome (NMS)

Patients and caregivers should be counseled that a potentially fatal symptom complex sometimes referred to as NMS has been reported in association with administration of antipsychotic drugs, including Olanzapine for Injection. Signs and symptoms of NMS include hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia) . *[see* **WARNINGS AND PRECAUTIONS ( ) 5.3***]*

17.4 Hyperglycemia

Patients should be advised of the potential risk of hyperglycemia-related adverse reactions. Patients should be monitored regularly for worsening of glucose control. Patients who have diabetes should follow their doctor's instructions about how often to check their blood sugar while taking Olanzapine for Injection . *[see* **WARNINGS AND PRECAUTIONS ( ) 5.4***]*

17.5 Hyperlipidemia

Patients should be counseled that hyperlipidemia has occurred during treatment with Olanzapine for

Injection. Patients should have their lipid profile monitored regularly . *[see* **WARNINGS AND PRECAUTIONS ( ) 5.5***]*

17.6 Weight Gain

Patients should be counseled that weight gain has occurred during treatment with Olanzapine for Injection. Patients should have their weight monitored regularly . *[see* **WARNINGS AND PRECAUTIONS ( ) 5.6***]*

17.7 Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration and in association with the use of concomitant drugs that may potentiate the orthostatic effect of Olanzapine for Injection, e.g., diazepam or alcohol AND . Patients should be advised to change positions carefully to help prevent orthostatic hypotension, and to lie down if they feel dizzy or faint, until they feel better. Patients should be advised to call their doctor if they experience any of the following signs and symptoms associated with orthostatic hypotension: dizziness, fast or slow heart beat, or fainting. *[see* **WARNINGS AND PRECAUTIONS ( ) 5.8DRUG INTERACTIONS ( ) 7***]*

17.8 Potential for Cognitive and Motor Impairment

Because Olanzapine for Injection has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Olanzapine for Injection therapy does not affect them adversely . *[see* **WARNINGS AND PRECAUTIONS ( ) 5.12***]*

17.9 Body Temperature Regulation

Patients should be advised regarding appropriate care in avoiding overheating and dehydration. Patients should be advised to call their doctor right away if they become severely ill and have some or all of these symptoms of dehydration: sweating too much or not at all, dry mouth, feeling very hot, feeling thirsty, not able to produce urine . *[see* **WARNINGS AND PRECAUTIONS ( ) 5.13***]*

17.10 Concomitant Medication

Patients should be advised to inform their physicians if they are taking, or plan to take, Symbyax . Patients should also be advised to inform their physicians if they are taking, plan to take, or have stopped taking any prescription or over-the-counter drugs, including herbal supplements, since there is a potential for interactions . ® *[see* **DRUG INTERACTIONS ( ) 7***]*

17.11 Alcohol

Patients should be advised to avoid alcohol while taking Olanzapine for Injection . *[see* **DRUG INTERACTIONS ( ) 7***]*

17.13 Use in Specific Populations

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with Olanzapine for Injection . *[see* **USE IN SPECIFIC POPULATIONS ( ) 8.1***]*

Nursing Mothers

Patients should be advised not to breast-feed an infant if they are taking Olanzapine for Injection . *[see* **USE IN SPECIFIC POPULATIONS ( ) 8.3***]*

Pediatric Use

Safety and effectiveness of olanzapine for injection in children and adolescents <18 years of age have

not been established.

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Manufactured by Gland Pharma Limited

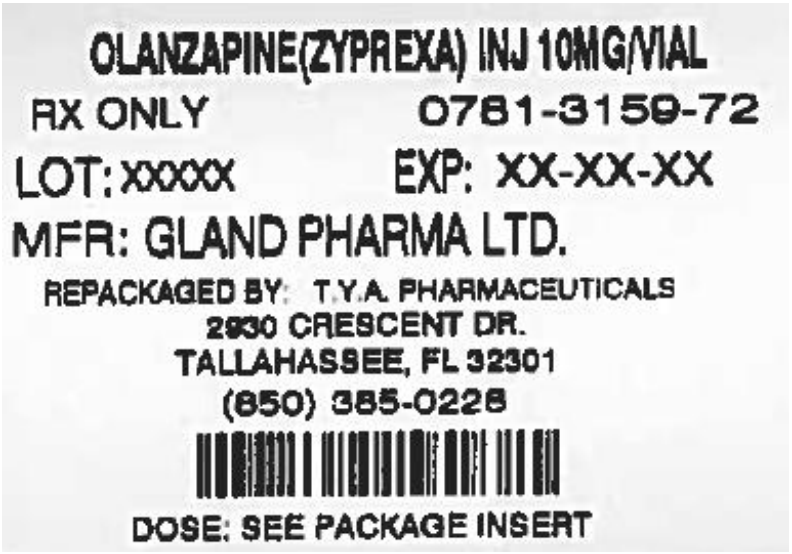
Hyderabad 500043, Andhra Pradesh, India

for Sandoz Inc.

Princeton, NJ 08540

M.L: 103/AP/RR/97/F/R

Revised: October 2011.



OLANZAPINE

olanzapine injection, powder, for solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:64725-3159(NDC:0781-3159)
Route of Administration	INTRAMUSCULAR		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
OLANZAPINE (UNII: N7U69T4SZR) (OLANZAPINE - UNII:N7U69T4SZR)	OLANZAPINE	10 mg in 2 mL

Inactive Ingredients	
Ingredient Name	**Strength**
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	50 mg in 2 mL
TARTARIC ACID (UNII: W4888I119H)	3.5 mg in 2 mL
HYDROCHLORIC ACID (UNII: QTT17582CB)	

SODIUM HYDROXIDE (UNII: 55X04QC32I)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:64725-3159-1	10 mL in 1 VIAL		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA201588	10/24/2011	

Labeler - TYA Pharmaceuticals (938389038)

Registrant - TYA Pharmaceuticals (938389038)

Establishment

Name	Address	ID/FEI	Business Operations
TYA Pharmaceuticals		938389038	RELABEL(64725-3159) , REPACK(64725-3159)

Revised: 11/2011 TYA Pharmaceuticals